of 166 pmol/L p=0·41 *vs* placebo).[8] Why all treated participants did not have increases in these hormones is unclear, but it must be remembered that if there is β-cell sparing in the responsive group, there must be a concomitant acceleration of β-cell loss in the non-responsive group.

As such, it remains plausible that some treatments that modify hormone concentrations might increase the resilience and expansion of β cells, and might have a role in stabilisation or remission of type 1 diabetes. Although DPP-4 inhibitors and GLP1-receptor agonists could be viewed as β-cell protective, they also increase the rate of insulin release. Of interest, this rationale might be contrary to the concept that those with newly diagnosed type 1 diabetes have injured β cells and would benefit from so-called β-cell rest via intensive glycaemic control; however, there is ongoing debate and conflicting data regarding this concept.[9,10]

Although non-immune-based treatments sound attractive for type 1 diabetes because they have few side-effects and might be supported by preclinical models, we are at a time when the data to move the field forward must come from more detailed study of type 1 diabetes in human beings. Future studies should take into consideration the findings of intervention trials of past decades, including negative trials such as REPAIR-T1D. From these studies, it is now seems evident that type 1 diabetes in human beings is a very robust autoimmune disease, for which potent immune-based treatment (alone or perhaps in combination with non-immune-based therapies) will be needed to arrest or slow β-cell loss.[3] The possibility also remains that other interventions (such as those studied in REPAIR-T1D) could augment that effect. However, before the autoimmune process of type 1 diabetes is controlled, other drugs that do not have proven direct immunomodulatory effects in human beings probably have low prospect of success for this disease.

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Low vitamin D and hypertension: a causal association?

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See Articles page 719

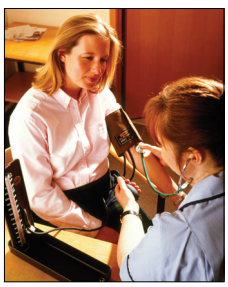
In *The Lancet Diabetes & Endocrinology*, Karani Vimaleswaran and colleagues[1] report the results of a mendelian randomisation study with data from up to 146 581 individuals, which suggest that low vitamin D concentrations might be causally associated with an increased risk of hypertension. The investigators used variants of genes that affect 25-hydroxyvitamin D (25[OH]D) synthesis or substrate availability (*CYP2R1* and *DHCR7*) and report that each 10% increase in genetically instrumented plasma 25(OH)D concentration was associated with a decrease in diastolic blood pressure (–0·29 mm Hg, 95%CI –0·52 to –0·07; p=0·01) and systolic blood pressure (–0·37 mm Hg, –0·73 to 0·003; p=0·052), and an 8·1% reduced odds of hypertension (odds ratio [OR] 0·92, 95% CI 0·87–0·97; p=0·002).

This study is timely, because a discrepancy exists between findings from observational studies and results of randomised intervention trials with respect to the relation between low vitamin D concentrations and increased risk of hypertension, with observational

findings suggesting a strong association and trial results showing no or only small effects.[2,3] Weaknesses inherent in observational studies such as reverse causation are a possible explanation for this difference—eg, individuals with hypertension might have more chronic diseases and therefore spend less time outdoors with sun exposure, important for endogenous vitamin D production. Another weakness is confounding; for example, obesity might account for the association between low vitamin D status and hypertension, because individuals with high BMIs have both low vitamin D concentrations[4,5] and an increased risk of hypertension.[6]

The mendelian randomisation approach used by Vimaleswaran and colleagues[1] circumvents reverse causation and largely excludes confounding.[7,8] This approach takes advantage of the random assortment of genetic variants that occurs during gamete formation, which secures an equal distribution of confounding factors among different genotypes. It can therefore be used to assess whether genetically affected risk factors are causally related to clinical outcomes. Thus, this design has similarities to a randomised intervention trial. Furthermore, genetic variants, like randomisation in a clinical trial, cannot be affected by diseases later in life and are therefore not prone to reverse causation. Thus, genetic variants that specifically decrease plasma 25(OH)D concentration (which is generally used to assess vitamin D status) can be used to assess the consequences of lifelong low 25(OH)D concentrations independent of other risk factors.

Vimaleswaran and colleagues' results have some limitations, however. First, since some of the reported p values are close to 0·05, the possibility that their findings are the result of chance cannot be excluded. Second, 25(OH)D-increasing genetic variants were associated with reduced hypertension as a binary outcome (OR per allele, 0·98, 95% CI 0·96–0·99; p=0·001), but only borderline associated with blood pressure on a continuous scale (–0·10 mm Hg [–0·21 to –0·0001; p=0·0498] for systolic blood pressure; –0·08 mm Hg [–0·15 to –0·02; p=0·01] for diastolic blood pressure), which is peculiar since the statistical power is typically higher for continuous than for dichotomised outcomes. Third, to be clinically relevant, 25(OH)D-increasing genetic variants should be causally associated with reduced risk of hypertension as well as with stroke, but the risk of stroke was not examined in the study. Finally, pleotropic effects represent a potential limitation in genetic studies—ie, genotypes might affect hypertension via a mechanism not directly related to low 25(OH)D concentrations—and such pleotropic effects are difficult to rule out completely.



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Randomised intervention trials are the gold standard to help establish causality, and must show a benefit before widespread vitamin D supplementation can be recommended for prevention or treatment of hypertension. However, with respect to understanding causality, the mendelian randomisation approach has two important differences from randomised intervention trials. First, the use of genetic variants that affect plasma 25(OH)D concentrations might capture the variation caused by one or more of the three potential sources of vitamin D (sun exposure, diet, and supplements), rather than the effect of supplements only, as assessed in randomised trials. Second, genetic studies examine lifelong exposure to 25(OH)D concentrations, rather than time-limited interventions. Thus, estimates from randomised intervention trials might be somewhat attenuated compared with estimates from mendelian randomisation studies.

Although Vimaleswaran and colleagues' study is an important step towards delineation of the role of low vitamin D concentrations in the pathogenesis of hypertension, much remains unknown. Confirmation of these results in independent, similarly powered studies will be necessary, as will evidence of a corresponding benefit for the prevention of diseases caused by hypertension such as stroke. Finally, randomised intervention trials will be needed to determine whether vitamin D supplementation can be used to prevent or treat hypertension before such a strategy can be used clinically.

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Combining incretin-based drugs and RAAS inhibitors: more cons than pros?

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Two novel antihyperglycaemic drug classes for the treatment of type 2 diabetes might have important, clinically relevant off-target effects. The so-called incretin-based drugs—ie, glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors—mainly reduce glucose concentration by improving pancreatic islet-cell function.[1] However, findings from clinical trials and preclinical studies suggest that incretin-based drugs have extra-pancreatic actions that interact with the renin-angiotensin-aldosterone system (RAAS; figure),[1] inhibitors of which are antihypertensive drugs taken daily by patients with type 2 diabetes.

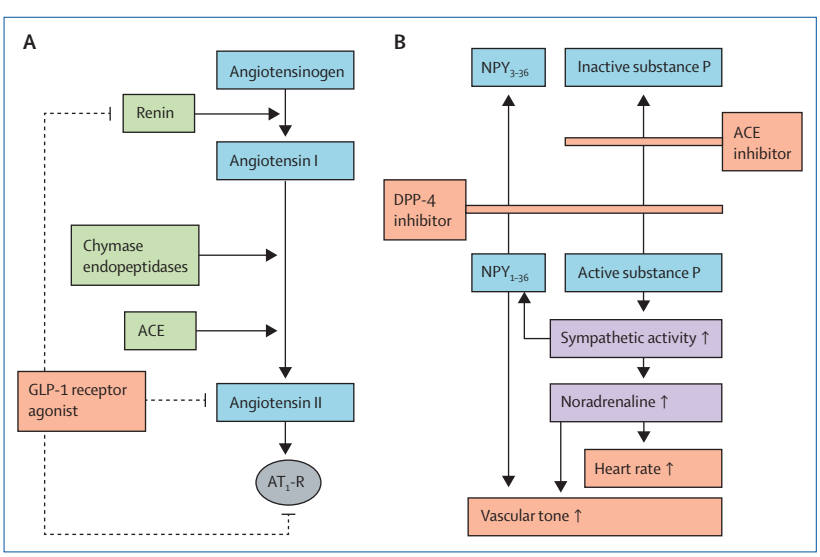

Figure: **Proposed interactions of incretin-based drugs with RAAS and the pharmacological compounds that interact with RAAS**
(A) Glucagon-like peptide-1 (GLP-1) might decrease circulating concentrations of angiotensin II, directly or through inhibition of renin production or release, in addition to inhibiting angiotensin II type 1 receptor (AT_1-R) after receptor activation (inhibition of ERK1 [MAPK3] and ERK2 [MAPK1] phosphorylation and NF-κB activation). (B) Dipeptidyl peptidase-4 (DPP-4) is the main cause of the inactivation of substance P when angiotensin-converting enzyme (ACE) is inhibited. Increased concentrations of active substance P during combined pharmacological inhibition might raise sympathetic activity, thereby increasing vascular tone and heart rate. Decreased DPP-4-mediated degradation of neuropeptide Y (NPY) might augment the vascular effect. RAAS=renin-angiotensin-aldosterone system.

Evidence from model systems[1,2] suggests that GLP-1 receptor activation inhibits intracellular signalling of the angiotensin II type 1 receptor, which mediates harmful effects of RAAS—such as inflammation and hypertension.[1,2] In healthy people, acute GLP-1 infusion lowers circulating angiotensin II concentrations by 15–19% and leads to a non-significant reduction in plasma renin activity.[2,3] In one study that included obese patients with glomerular hyperfiltration,[3] 25% of whom had type 2 diabetes, GLP-1 infusion reduced plasma renin activity by 25% (figure). The reduced renin secretion might be accounted for by a direct effect of GLP-1 on the juxtaglomerular cells,[4] via atrial natriuretic peptide,[1] or through inhibition of tubuloglomerular feedback by inhibition of proximal sodium reabsorption.[1,2] Skov and colleagues[2] hypothesised that many GLP-1-mediated effects on RAAS—including glucose-dependent insulin secretion, renoprotection, and inhibition of the Na^+/H^+ exchanger isoform 3 in the proximal tubule—are partly caused by decreased angiotensin-II signalling. Stronger inhibition of the RAAS cascade by GLP-1 receptor agonists might further increase the protective effects of compounds that interact with RAAS. However, the clinical benefit of such augmented inhibition could be questionable in view of the results of the ONTARGET, ALTITUDE, and the recently stopped VA NEPHRON-D trials, which showed increased risk of adverse events, including hyperkalaemia and renal failure, when two different drugs that synergistically inhibit RAAS were combined.[5] As a result, dual RAAS blockade in patients with diabetes is currently not recommended.[5] Notably,